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The role of γ-scintigraphy in oral drug delivery☆

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Abstract

The gastrointestinal tract is usually the preferred site of absorption for most therapeutic agents, as seen from the standpoints of convenience of administration, patient compliance and cost. In recent years there has been a tendency to employ sophisticated systems that enable controlled or timed release of a drug, thereby providing a better dosing pattern and greater convenience to the patient. Although much about the performance of a system can be learned from in vitro release studies using conventional and modified dissolution methods, evaluation in vivo is essential in product development. The non-invasive technique of γ-scintigraphy has been used to follow the gastrointestinal transit and release characteristics of a variety of pharmaceutical dosage forms. Such studies provide an insight into the fate of the delivery system and its integrity and enable the relationship between in vivo performance and resultant pharmacokinetics to be examined (pharmacoscintigraphy).

Keywords: In vivo performance; Regulatory approval; Gastrointestinal transit; Drug absorption; Pharmacoscintigraphy; Imaging procedure

Contents

Abbreviations: ACE, angiotensin-converting enzyme; ADME, absorption, distribution, metabolism and excretion; CBZ, carbamazepine; DTPA, diethylenetriaminepentaacetic acid; CR, controlled release; GI, gastrointestinal; GIT, gastrointestinal tract; ICJ, ileocaecal junction; IR, immediate release; MMC, migrating myoelectric complex; MU, multiple unit; RTC, radiotelemetry capsule; SI, small intestine; SIT, small intestinal transit; SR, sustained release; SU, single unit; USP, United States Pharmacopoeia

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1. Introduction

Drug compounds are not usually administered to patients as such but are given as formulated medicines, for example, a tablet, capsule, suppository, aerosol, etc. In developing these medicines, it is most important to establish that any optimized system will perform correctly; moreover, extensive testing is required before a new product can be submitted to a regulatory authority for approval. Many of these tests can be performed in vitro but certain essential measurements have to be conducted in healthy volunteers and patients.

Despite a rapid growth in the novel routes for drug delivery, the vast majority of therapeutic agents are still administered orally. Many oral dosage forms are designed to disintegrate rapidly in the stomach. However, there is a growing trend to use sophisticated systems that enable controlled or timed release of a drug, thereby providing a better dosing pattern and greater patient convenience. These modified release systems are, by necessity, more complicated than conventional tablets and capsules and require new methods for their evaluation. Reliance on pharmacokinetic measurements (the appearance of the drug in the bloodstream) may be unreliable, since they indicate solely the result of drug release and not the responsible mechanisms.

New proposals from the regulatory authorities of both Japan and the USA, for controlled release (CR) oral dosage forms require submitting organisations to provide information about the performance of a new product within the gastrointestinal tract (GIT) (Table 1). Only a limited number of methodologies is

Table 1
Quotes

Source	Section	Quote
Report on the Workshop on Modified Release Dosage Forms Sponsored by The American Association of Pharmaceutical Scientists, FIP USP, and FDA, December 1988	Pharmaceutical Considerations 1. Understanding the delivery system	Sponsor should explain the rationale for the dose selected and the dosage form. It must be demonstrated that the dosage form performs in vivo according to its proposed rationale
Guidelines for the Design and Evaluation of Oral Prolonged Release Dosage Forms	Notification No. 5 of 1st Evaluation and Registration Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, Japan, 1988. 1.2.1. Transit characteristics of the dosage form through the gastrointestinal tract	The transit rate of a dosage form through the gastrointestinal tract is known to depend on the size, form, specific gravity, and adhesiveness of the preparation; physiologically on the length, form, position, and motility of the gastrointestinal tract; and on the composition and volume of the gastrointestinal contents. It is also affected by food, pathology, posture and stress. The bioavailability of a candidate drug often depends on the gastrointestinal transit rate of the dosage form. Therefore, the travelling characteristics of the dosage form through the gastrointestinal tract should be fully considered in designing the best possible dosage form.

currently available to provide such data. The objectives of this article will be to review critically the relative merits of the different techniques available for assessment of in vivo performance, to discuss the fate of oral dosage forms in vivo and to provide specific case histories detailing the role of scintigraphic evaluation in oral drug delivery.

2. Methodology

2.1. Endoscopy

Since the development of a prototype fiberscope in 1975, the evolution and refinements in Japanese technology have resulted in various fiberscopes, perfectly adapted for the diagnosis of upper gastrointestinal (GI) diseases [1]. In fact, endoscopy is now routinely used as the diagnostic procedure of choice, whereas radiology is used secondarily, with the indications determined by the endoscopist. Recent advances have also led to the development of therapeutic endoscopy which is routinely used in emergency situations, e.g. hemorrhage [2], neoplasia [3], nutritional assistance [4] and in other GI disorders. Sedation is widely used in diagnostic gastroscopy but it is not critical to the performance of the procedure [5]. However, there is general agreement that patient tolerance and comfort are improved by sedation which can make the procedure easier to perform for the endoscopist.

Use of endoscopy in the evaluation of oral dosage forms has been largely restricted to studies on their performance in the stomach. In particular gastroscopic analysis has been shown to be useful in the evaluation of various antibiotic capsules and tablets, e.g. pivmecillinam and pivampicillin, where poor tolerance to the drug has been related to the disintegration characteristics of the dosage form [6,7]. Spreading of the tablet/capsule contents is often related to drug-induced interstitial bleeding or mucosal erosion. Similar studies have also been carried out on various formulations of potassium chloride [8,9]. Endoscopic analysis has recently been used to examine the in vivo mucoadhesive properties of various polymeric systems with interesting results [10].

Although endoscopy provides a real-time visual examination of dosage form interaction with the mucosal tissue, there are major disadvantages. In particular, the invasive nature of the endoscopy procedure can cause significant discomfort to the subject and, although this can be relieved by the use of sedatives and local anesthetics, subject acceptability is far from high. The pharmacological effects of the pre-medication drugs, which include intravenous diazepam, on GI function are also difficult to predict. The presence of the endoscopic probe may itself cause abnormal behaviour of the solid dosage form.

2.2. Radiotelemetry (pH)

With the advent of stable, reliable pH capsules, it is now possible to monitor pH in the GIT with a greater degree of accuracy than was possible previously. With the introduction of portable receiving apparatus, GI pH can be measured while patients carry out their normal daily activities. Capsule position in the GIT can be monitored by surface location using a directional detector or by attachment of a suitable radiopharmaceutical to the pH capsule which allows accurate localisation using γ-scintigraphy [11–14]. In a group of 66 subjects, Evans et al. [15] have shown that gastric pH is highly acidic in the fasted state (range 1.0–2.5). The mean pH in the proximal small intestine (SI) was 6.6 ± 0.5 for the first hour of intestinal reading; mean pH in the terminal ileum was 7.5 ± 0.4. In all subjects there was a sharp fall in pH of about 1 pH unit to a mean of 6.4 ± 0.4, as the capsule passed into the calcium, presumably due to the production of short-chain fatty acids from bacterial fermentation of dietary fiber. pH then rose progressively from the right to the left colon with a final value of 7.0 ± 0.7. Similar trends have been shown by other workers [11,13,14,16]. However, other groups using the less sensitive Heidelberg radiotelemetry capsule (RTC), which is prone to drifting at later time points, have shown a rise in pH across the ileo-caecal junction (ICJ) [12].

The combination of γ-scintigraphy and telemetry for pH measurements can provide additional information about the in vivo performance of oral dosage forms, in particular enteric coated systems [11,13]. Information about the pH of the microenvironment around the dosage form can only be

inferred if the RTC is in close proximity to the dosage form. However, the monitoring device and the dosage form may not be in the same anatomical region after gastric emptying due to the complex nature of small bowel anatomy and the different transit profile of the systems [14].

The rapid rise in pH as the RTC leaves the stomach (Fig. 1) has been used to evaluate the effects of food, gender, posture, age and concurrently administered drugs, on the gastric residence time of the non-disintegrating formulation [12,17–20]. This approach can only be extrapolated to concomitantly administered oral dosage forms if the two systems are tethered together. Such a procedure was recently described by Chan et al. [21] in a study to evaluate the absorption of diclofenac sodium after oral administration of both enteric coated and sustained release (SR) formulations. Prior to administration, a 0.4-mm hole was drilled through the centre of the enteric coated and SR tablets. Surgical thread was then looped through this hole and secured in place, using a small amount of acrylic glue on both faces of the tablet. No change in the in vitro dissolution behaviour under USP conditions was noted for the tethered system compared with the untreated formulations. The variability of individual plasma concentrations was substantially reduced when the time after dosing was adjusted to coincide with gastric emptying of the tethered formulation. In addition, the absorption lag time for the SR formulation coincided with its gastric residence time. This study demonstrates the value of the combined use of pharmacokinetics and techniques suitable for the assessment of GI transit. However, it is highly probable that the tethering of the radiotelemetry device to dosage forms will in fact alter their in vivo performance. Recent studies have shown that tablets up to 11 mm can leave the fed stomach prior to the onset of fasted activity [22–24]; however, this is in marked contrast to radio-telemetry devices which are

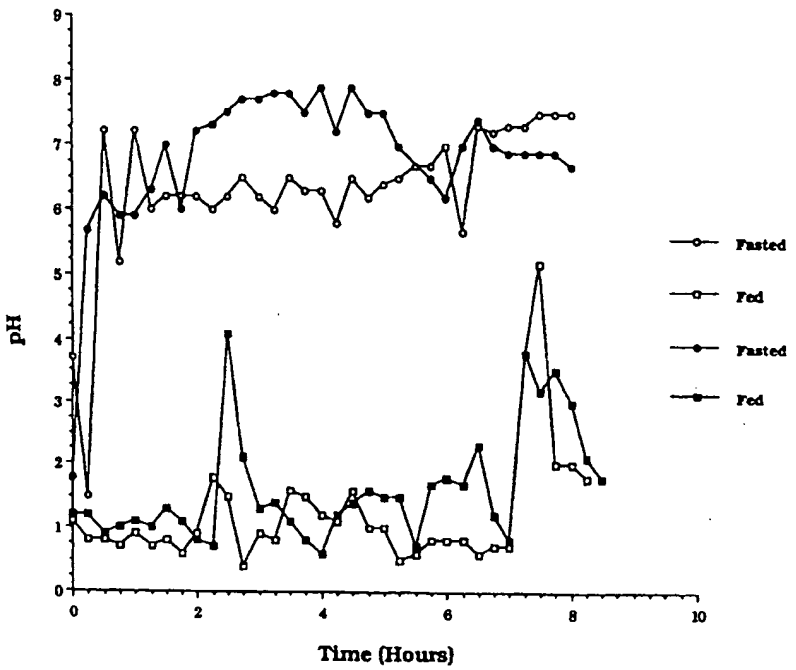

Fig. 1. Composite pH profile of four consecutive administrations of a radiotelemetry capsule after either an overnight fast or a light breakfast [14].

retained in the stomach and are only emptied by the large phase III contractions of the migrating myoelectric complex (MMC) [25].

2.3. Radiology (X-rays)

Radiological assessment has been used for many years to provide both a qualitative and a semi-quantitative assessment of motor behaviour in the different segments of the alimentary canal, e.g. oesophageal motility [26], gastric emptying [27], small intestinal transit (SIT) [28] and colonic transit [29].

The inclusion of a radio-opaque material into an oral drug delivery system to evaluate its in vivo behaviour by radiological procedures was first reported by Losinsky and Diver in 1933 [30]. Similar approaches have been used by subsequent workers to characterise the in vivo disintegration properties of oral dosage forms [31,32] and also the oesophageal transit of capsules [33]. Only comparatively recently has the use of X-ray procedures been adapted to the evaluation of SR dosage forms. Galeone et al. [34] conducted a study on the performance of pelletized oral dosage forms containing soluble (iodamide) and insoluble (barium sulphate) contrast medium. The combined use of radiology and pharmacokinetics has been used to examine the relationship between dosage form position and subsequent absorption of verapamil for both a single unit (SU) tablet preparation [35] and a multiparticulate formulation [36]. The SU device was labelled by the inclusion of a hollow stainless steel ball (2 mm diameter) in the tablet core and for the multiparticulate study, the verapamil pellets were mixed with coated barium sulphate pellets of a similar particle size and density. The distribution of SR ketoprofen pellets in various segments of the GIT has also been examined by the use of X-ray procedures in a very limited study [37].

Radiological studies can provide information on the transit of dosage forms throughout the GIT and can also yield useful detail on anatomical structure. However, these studies suffer from three major disadvantages: to assess accurately GI transit the subjects must be exposed to the repeated risk of serial X-rays, the necessity to modify the physical state of the dosage form in order to make it radio-opaque, and the data collected are qualitative.

2.4. Epigastric impedance

Impedance methods are now established as non-invasive and accurate for the monitoring of organ volume. The technique measures the impedance in a cross-section through the body. Four electrodes are used: two are placed anteriorly and two posteriorly over the gastric region. An alternating current of 4 mA at 100 kHz is applied through one anterior and one posterior electrode and the remaining two electrodes record the change in voltage [38]. The technique is used clinically as a simple, cheap alternative to scintigraphy, for the detection of changes in gastric emptying. The technique has been used to measure the effect of drugs on gastric emptying in normal volunteers. Sutton and McCelland [39] reported faster gastric emptying after an intravenous dose of metoclopramide in healthy volunteers using the simple four-electrode device.

Both epigastric impedance and its sister technique, applied potential tomography, are comparatively new approaches to the characterisation of GI function. To date they have not been used to evaluate oral delivery systems per se, with the exception of the prokinetic studies described above. However, current advances, designed to improve the resolution of the technique, may enable the approach to be adapted for the in vivo characterisation of certain delivery systems, in particular non-disintegrating SU dosage forms.

2.5. Ultrasonography

Ultrasonic imaging has been employed increasingly for visualising internal body structures since the early 1970s. It is non-invasive and safe, although in experiments ultrasound has been associated with adverse biological effects produced by thermal damage to tissues and cavitation [40]. An ultrasonic image is formed when a beam of very-high-frequency sound impulses (1.5–10 MHz) is sent into a subject and is reflected back to a varying degree depending on the density of the medium through which it is passing. The approach is used clinically

for both the measurement of antral emptying rate and for providing an assessment of antral and transpyloric fluid motion [41]. The technique has recently been utilised in a pilot study to assess the shape and size of a tablet in the stomach [42] with a view to using the approach for the future assessment of bioadhesive dosage forms.

2.6. γ-Scintigraphy

The technique of γ-scintigraphy has become the most popular method to investigate the GI performance of pharmaceutical dosage forms. Although used for many years by GI physiologists [43], it was only in 1976 that the fate of pharmaceuticals in vivo was first investigated by this approach [44,45].

The head of a γ-camera commonly consists of a large sodium iodide crystal, 40 cm in diameter, activated with thallium, NaI (Tl), to promote scintillation properties. The thickness of the crystal is restricted to approximately 10 mm to optimise the detection efficiency. Coupled to the crystal is an hexagonal array of photomultiplier tubes which detect the light pulses. The whole arrangement is encased in lead to shield the crystal from extraneous radiation. An electronics package links the photomultiplier tubes to a computer and visual display unit. A lead collimator placed directly in front of the crystal enables the γ-rays to be focused onto the detector. The most commonly used collimators, parallel-hole, give a 1:1 correspondence of object and projection onto the scintillator [46]. The collimator consists of many thousands of parallel-sided holes which ensure that only parallel rays emitted from the source are detected. Different thickness of septa are available, depending on the photon energy of the isotope. Further information about the γ-camera can be found in the following texts [47,48].

Choice of a suitable radionuclide for scintigraphic studies can be ascertained by considering factors such as the radiation energy, half-life, extent of particulate radiation, cost and availability. Metal ion nuclides most closely satisfy these essential criteria and hence their extensive use in scintigraphic studies. The most popular of these metal ion nuclides is ^{99m}Tc with its versatile chemistry, near-ideal energy (140 keV), low radiation dose and short half-life (6 h). In addition, it is readily available through the use of portable generators. Other commonly used metal-ion nuclides include ^{111}In and ^{113m}In.

Once a decision about a suitable nuclide has been made, an appropriate agent must be selected to carry the isotope. GI studies sometimes require both solid-phase and liquid-phase markers. Radiopharmaceuticals labelled with ^{99m}Tc are the most widely used, due to the advantages of the isotope, and include chelating agents such as diethylenetriaminepentaacetic acid (DTPA) [49], colloids such as sulphur colloid [50], cells and blood elements [51] and cellulose macromolecules [52].

There are two basic approaches for the conventional labelling of oral dosage forms. One method is to incorporate a non-absorbable chelate of the radioactive isotope, e.g. ^{99m}Tc-DTPA [53]. The other method involves the incorporation of a radiolabelled ion-exchange resin [54]. In many cases, the latter method is preferable, since the resin remains within the device so that the position in vivo can be observed. These conventional methods of labelling require the marker to be incorporated as late as possible to minimise the risk of radioactive contamination. In many cases, the manufacturing process must be scaled down to lower the amount of radiation handled which can in some cases significantly alter the behaviour of the dosage form.

These problems can be overcome by the use of stable isotopes and neutron activation methods [13,55–60]. A stable isotope (e.g. ^{170}Er or ^{152}Sm, as the isotopically enriched oxide) can be incorporated into the dosage form at a low level and the product irradiated in a neutron source to convert the isotope into a γ-emitting material (i.e. ^{171}Er or ^{153}Sm). These nuclides possess large neutron capture cross-sections, and can be obtained in highly enriched forms, which in turn improves the radionuclidic purity of the final dosage form. The radiation exposure to a subject following dosing with these radionuclides is comparable to that received using conventional radiolabelling with ^{99m}Tc and ^{111}In. By using these neutron activation methods, radiation levels can be minimised, quality assurance maintained, and complicated delivery systems labelled easily and efficiently.

Certain inherent errors exist with the technique of γ-scintigraphy. These are related to the physical properties of the radionuclides and instruments or the

distribution of the radionuclide within the subject. A simple subtraction of the background count from the gross count will give the net count from the source alone [48]. Natural radioisotopes, cosmic rays and instrument noise are common causes of background activity. Correction for radioactive decay is necessary for accurate results in GI transit studies, since the timescale for imaging is normally long.

Radiation from ingested isotopes is scattered or absorbed by intervening tissues and bone, before reaching the γ-camera, causing the radiation registered to be attenuated. Therefore, both anterior and posterior images are taken at each time interval and the geometric mean of the counts calculated [61]. This procedure corrects for the problem of anterior movement of the radiopharmaceutical during gastric emptying studies, since the antrum lies more anterior than the fundus.

3. Gastrointestinal physiology and oral dosage forms

Much of the early scintigraphic research examined the interaction of the dosage form with the GIT and probed relevant issues about the in vivo fate of oral delivery systems (Table 2). The information available in the literature at the time was either unhelpful or even misleading. For example, one report suggested that SIT could be as long as 8 h [99]. This is now known to be at least a 2-fold overestimation [75] and that longer transit times, in excess of 4 h, are in fact very rare, except possibly following nighttime administration [83,91]. Over the last decade the pharmaceutical industry has realised the importance of GI transit in the rational design of oral delivery systems. However, a number of misconceptions still abound in the literature and a review of the salient facts will provide further evidence of the importance of γ-scintigraphy in this re-education process.

3.1. Gastric emptying

It is well known that the stomach behaves in two discrete ways, depending on whether it contains food or is empty [100]. The primary function of the distal stomach (antrum) is to mix and triturate gastric contents, and then to discharge the partially digested material (the chyme) into the proximal SI. The stomach can empty small particles of food while retaining large undigested material by an 'antral-

Table 2
Issues relevant to the gastrointestinal transit of oral drug delivery systems

Buccal cavity	Release characteristics of controlled-release systems to include matrix tablets and chewing gum [62–64]
Oesophagus	Transit studies of pharmaceutical dosage forms [65–67]
Transit measurements through the stomach and intestines	Gastric emptying, small intestinal, colonic and total transit of dosage forms [23,24,68–79]
	Studies of the physiological factors likely to affect gastrointestinal transit of dosage forms, e.g. age, posture, time of dosing, exercise, bed rest [80–83]
	Pharmaceutical strategies intended to prolong gastrointestinal transit; e.g. dosage form size, shape and density [22,84–89]
	Effects of pathophysiology on gastrointestinal transit, e.g. irritable bowel syndrome, inflammatory bowel disease [90,91]
	Combination of transit studies with measurements of pH and motility [11,13,14]
	Differential transit behaviour of single and multiple-unit dosage forms [92–94]
	Disintegration rate of capsules and tablets [44,45,95,96]
	Putative bioadhesives intended to change gastrointestinal transit [97,98]

sieving' process. In the fed state, stomach contractions move the contents towards the distal antrum and the pyloric sphincter. Liquids and small particles of food are capable of passing through the partially constricted pylorus while the larger units are retropelled into the main body of the stomach. Non-digestible material is unable to leave the stomach while it remains in the fed state. At the end of the digestive period the stomach enters a different period of activity known as the interdigestive myoelectric cycle or MMC [101].

During fasting, the stomach normally contains swallowed saliva, mucus and cellular debris. In addition, there may be large particles of indigestible food left from the previous meal. The MMC will empty these contents and consists of four consecutive phases of activity [102]:

phase 1 — a period of quiescence lasting about 60 min with no contractions;
phase 2 — about 40 min of intermittent action potentials and contractions that gradually increase in intensity as the phase progresses;
phase 3 — a short phase of intense distal and proximal gastric contractions lasting between 5 and 15 min; these contractions, also known as the 'housekeeper' wave, completely empty the stomach;
phase 4 — a short transitory period between the intense activity of phase 3 and quiescence of phase 1.

The different phases of the cycle migrate distally from the stomach to the terminal ileum over a 2-h period. Therefore, when one phase 3 reaches the terminal ileum, another one is beginning in the stomach. On feeding, the cycle is immediately broken with a normal meal disrupting the activity for approximately 3–4 h.

Oral dosage forms can take many shapes and forms, but in general, they can be divided into two categories: multiple-unit (MU) systems and SU devices [103]. MU preparations are composed of many individual SR subunits, such as pellets [104] or small tablets [104], administered in a hard gelatin capsule or as a rapidly disintegrating tablet. SU preparations traditionally remain intact as a non-disintegrating unit throughout the GIT.

Two main parameters influence gastric emptying of SR dosage forms: the physical size of the delivery device and whether or not it is administered to a fed or fasted stomach [54]. Large SU tablets or capsules are treated by the stomach as indigestible material and are emptied along with the phase-3 activity of the MMC [70]. If the stomach is maintained in the fed mode by a process of continuous feeding then the SU device will be retained during that time period. Prolonged gastric retention may be of therapeutic advantage if the major absorptive sites for the drug are in the proximal SI. Interestingly, when two large SU dosage forms (12-mm tablets) are administered simultaneously they can empty from the fed stomach at about the same time or at widely different times [77]. This variability has clear implications for the bioavailability of the drug contained therein. In the fasted state, large tablets empty in an erratic manner, depending on their time of arrival in the stomach in relation to contractile activity of the MMC [105].

Recent combined scintigraphic and radiotelemetry motility studies [25] have confirmed that large SU devices, such as a RTC, are only emptied from the stomach by the large phase-3 contractions of the MMC. However, gastric emptying under the control of phase-3 contractions is not always efficient. For instance, in one subject, the RTC (25 × 8 mm) was retained in the stomach for over 12 h, during which time three distinct phase-3 complexes were monitored at 4.5, 6.5 and 8.5 h post-dose. The subject's gastric emptying time for the radiolabelled meal was 2.5 h, therefore indicating a 2-hourly recurring MMC. No additional food was administered until the end of the study period. It has been suggested that the RTC remained in the less muscular body of the stomach and was not propelled into the antrum of the stomach where emptying could take place. Similar results have been observed for pH telemetry devices [17] and large non-disintegrating pharmaceutical dosage forms [22,88,105].

MU formulations composed of a myriad of 1-mm pellets have been found to pass through the constricted pylorus leading to a gradual emptying of the subunits [69]. Such gradual emptying ensures that the subunits are well dispersed in the SI and mini-

mises the potential for mucosal irritation [104]. However, the initial gastric dispersion of the subunits is dependent on the physiological condition of the stomach at the time of administration.

In the fasted state, there is only a limited dispersion of the subunits and a bolus emptying of material occurs which has been observed for both powders [95] and pellets [73,76]. Pellet systems, when taken with or after a light meal (1000–2000 kJ), exhibit a short lag phase before the commencement of a linear emptying pattern [106]. The administration of an encapsulated pellet system, after a very heavy breakfast (5000 kJ), has been shown to markedly enhance gastric residence [36]. Although small portions of the pellets emptied with the solid phase of the food, the great majority remained in the stomach up to 6–8 h prior to the action of the 'housekeeper wave'.

Khosla and co-workers [22,88] have tried to determine the size cut off point for antral sieving. Surprisingly, it was found that tablets up to 11 mm diameter can empty from the fed stomach in an apparently linear fashion. An increase in the variability of emptying, as tablet size increased, was noted but no significant differences in gastric emptying due to tablet size could be found. The results of this work, and that of others [94,107], indicate that the much discussed 2-mm cut-off size for the gastric emptying of indigestible solids during the digestive phase in canines [108] is not applicable to man. Moreover, it has been found that the presence of food is far more important than tablet size; the greater the calorific value of the meal, the longer the duration of emptying.

It has been suggested that control of gastric emptying may be useful in the development of SR dosage forms [109]. Strategies proposed for this purpose include particle density [84,89], floating devices [85,110,111] and bioadhesives [97,98,112]. Only limited success has been achieved however.

3.2. Small intestinal transit

The scintigraphic technique is not particularly useful in defining anatomical detail, particularly that of the SI and unlike radiography, it is normally impossible to delineate loops of the intestine. However, the presence of the dosage form in the stomach and its subsequent gastric emptying can be well defined. Its arrival at the caecum is also easy to assess and therefore it is possible to evaluate SIT by the difference. For an SU system, SIT is taken as the difference in time between leaving the stomach and arrival at the caecum. For an MU preparation, which may empty from the stomach over an extended period of time, especially when administered with food, it is normal practice to take the time for 50% gastric emptying and the time for 50% colonic filling and to use the difference between these values as the SIT time.

Scintigraphic evaluation of a large number of diverse formulations has shown a remarkable degree of consistency in the data reported for SIT with a mean transit time of 3–4 h with a standard deviation of 1 h [75]. This finding was independent of the type of dosage form, i.e. solutions, pellets, small tablets, large SU devices, etc., and was not statistically different in the fasted or fed state. No attributable differences can be made to age or pathological conditions such as ulcerative colitis, diarrhoea, or constipation. Eating has been shown to have no effect on small bowel transit [78]. Subjects either remained fasted after dosing or consumed a standard meal at different times after receiving the test preparation. Transit rates have also been shown to be unaffected by exercise [82].

The relatively short residence time in the SI has implications for the design of SR dosage forms. If a drug is not well absorbed from the colon, then once-a-day therapy from a single dosage administered in the fasted state may be impossible to achieve, unless the drug has a relatively long half-life.

Recent studies [23] have investigated the inter- and intrasubject variability in gastric emptying and SIT for SU and MU formulations. Variability in gastric emptying of both systems was large, the intrasubject variation being less than the intersubject. Less variation was reported in SIT times compared with the gastric emptying data, with intrasubject variation being less than the intersubject variation. The results may be anticipated considering the multiplicity of factors that influence transit of materials throughout the GIT.

3.3. Colonic transit

Transit of dosage forms from the ileum to the caecum and proximal colon across the ICJ is a poorly understood event [113]. It appears that subunits of a MU device can regroup at the ICJ before entering and subsequently spreading in the colon [24,79]. This stagnation effect may be related to the proposed reservoir function of the terminal ileum [114]. The knowledge that pellets, or 'small' tablets, can become widely dispersed within the colon has led to the development of MU systems for the delivery of 5-aminosalicylic acid to the colon for the treatment of ulcerative colitis [115]. The extent of dispersion is size dependent, since large particles pass through the colon more rapidly than smaller particles [73,87]. Further work is necessary in this area to fully elucidate the role of the ICJ in controlling transit of dosage forms from the terminal ileum to the large bowel.

The effect of dietary fibre on the GI transit of a SU and a MU dosage form in vegetarians and omnivores has recently been investigated using the technique of γ-scintigraphy [24]. Subjects were fed on a strict diet containing either 15 or 40 g of dietary fibre for at least 6 days prior to each study day to allow the GIT to become accustomed to the new diet. Gastric emptying of both the types of dosage form was found to be unaffected by fibre content of the diet; however, SIT appeared to be longer in vegetarians than omnivores, irrespective of fibre intake. Transit time of the dosage forms within each region of the colon was highly variable; however, overall transit time in the vegetarians was slower than in the omnivores.

4. Pharmacoscintigraphy

The combination of scintigraphy with pharmacokinetic studies (pharmacoscintigraphy) has now become an important means of providing information about the transit and release behaviour of oral dosage forms and subsequent drug absorption. Prototype delivery systems, such as the OSMET™ device from the ALZA Corporation (CA, USA) and the PULSINCAP™ from Polysystems (Scotland) can be used to evaluate drug absorption resulting from zero order and pulsatile delivery, respectively. Table 3 summarizes the various studies that have been performed where scintigraphy and pharmacokinetics have been combined to study orally administered dosage forms. Some recent case histories from our own group will be described in more detail to illustrate the methodologies employed, the labelling procedures used and the results obtained.

4.1. Evaluation of an enteric-coated naproxen pellet formulation (Ref. [13])

Damage to the gastric mucosa caused by non-steroidal drugs can be reduced by enteric coated formulations. The enteric coating is insoluble in the normal acid conditions of the stomach but dissolves once the product enters the small intestine. Residence time in the stomach will have an important role on the performance of such a system. It is also to be expected that a large SU device will provide a variable response, since gastric emptying will be very dependent on food intake. An MU system that can empty from the stomach in the presence of food is often preferred. The objective of the study was to evaluate an enteric coated naproxen pellet formulation.

Pellets 0.8–1.2 mm in diameter were provided with an enteric coating insoluble below pH 6.5. Each dose of coated pellets contained 2 mg samarium oxide and was radiolabelled by neutron activation, resulting in 1 MBq of ^{153}Sm per capsule at the time of dosing. In vitro studies demonstrated that neither the addition of the samarium oxide nor the neutron activation process affected the performance of the product nor the stability of the drug. Eight volunteers were dosed with the labelled product on two occasions, once while fasted and once after a light breakfast. Each subject also received the non-radiolabelled uncoated pellets while fasted to provide control data. GI transit was followed using γ-scintigraphy. The pH in the stomach and intestines was monitored using an RTC capsule. Transit of the labelled pellets dosed to the same subject under fasted and fed conditions is shown in Fig. 2. Median plasma concentrations are shown in Fig. 3. Gastric emptying was delayed by dosing after breakfast but

Table 3
Studies using the combined approach of pharmacokinetics and scintigraphy (pharmacoscintigraphy) for the evaluation of oral dosage forms*

Authors (Year) [Ref.]	Drug	Formulation	Label	Subject	Dietary state	Objectives	Pharmacokinetic data
Ganley et al (1984) [116]	Glibenclamide	C	^{99m}Tc DTPA	4M-H	Fa/LB	Correlation of capsule dispersion to drug absorption	Absorption observed after dispersion in the small intestine
Wilson et al. (1984) [117]	Aspirin	T	^{99m}Tc DTPA	5M-H	LB	Correlation of dosage form position to serum concentration	In vivo confirmation of sustained release properties of formulation
Davis et al. (1986) [118]	Naproxen	T	^{111}In resin	6M/6F-H	LB/HB	The effect of food on the transit of tablets in old and young	No pharmacokinetic data reported
Davis et al. (1987) [106]	Tiaprofenic acid	MU	^{99m}Tc resin	6M-H	LB/HB	Influence of food on transit	No pharmacokinetic data reported
Fisher et al. (1987) [119]	Isosorbide-5-nitrate	MU	^{111}In DTPA	6M-H	MB	Correlation of dosage form position to serum concentration	Good absorption from the stomach and small intestine but reduced from the colon
Hardy et al. (1987) [11]	Naproxen	T	^{111}In resin	6M-H	MB	Tablet disintegration and onset of absorption	Close correlation between tablet coat disruption and detection of drug in plasma
Hardy et al. (1987) [120]	5-ASA	T	^{111}In resin	8M-H	FaLB	Tablet disintegration and onset of absorption	Close correlation between tablet coat disruption and detection of drug in plasma
Hardy et al. (1987) [121]	5-ASA	T	^{111}In resin	7M/6F-P	LB	Tablet disintegration and onset of absorption	Close correlation between tablet coat disruption and detection of drug in plasma
Maublant et al. (1987) [122]	Theophylline	T	^{99M} Tc DTPA	6M-H	Fa	In vitro–in vivo correlation	Close correlation between in vivo dissolution rate of both marker and drug
Parr et al. (1987) [58]	Ibuprofen	T	^{171}Er oxide	8M-H	Fa	Correlation of dosage form position to serum concentration	Tablet erosion and absorption throughout the GI tract
Ulmius et al. (1987) [123]	Enprofylline	T	^{99m}Tc sulph. coll.	6X-H	Fa/B	In vivo dissolution and correlation between position and absorption	Upper GI tract absorption governed by dissolution from tablet, whereas in the colon rate-limiting step was absorption
Wilson et al. (1987) [124]	Acyclovir	S	^{99m}Tc resin	6M-H	LB/HB	The influence of food on the absorption of acyclovir	The heavier meal slowed GI transit and decreased drug absorption
Davis et al. (1988) [125]	Oxprenolol	O	^{99m}Tc DTPA	6M-H	Fa	Correlation of dosage form position to serum concentration	Drug absorbed throughout the GI tract
Soumac et al. (1988) [126]	Theophylline	T	^{99m}Tc DTPA	6M-H	Fa	In vitro–in vivo correlation	Correlation of absorption data with in vitro release kinetics
Davis et al. (1989) [127]	Aminophylline	T	^{99m}Tc E-HIDA	6X-H	LB	In vitro–in vivo correlation and relationship of dosage form position to serum concentration	Absorption of drug independent of tablet position and controlled by release from the tablet
Feely et al. (1989) [94]	Phenylpropanolamine	T/MU	^{111}In resin	6M-H	LB	Comparison of formulation bioavailability	Plasma levels unaffected by the variable transit of the formulations
Li et al. (1989) [128]	Metoprolol	T	^{131}In resin	6X-H	–	Pharmacokinetic study	Absorbed dose correlated with in vivo dissolution rate
Maublant et al. (1989) [129]	Theophylline	T	^{99m}Tc DTPA	6M-H	Fa/MB	In vitro–in vivo correlation	Food increased transit time but had no effect on bioavailability

Table 3. Continued

Authors (Year) [Ref.]	Drug	Formulation	Label	Subject	Dietary state	Objectives	Pharmacokinetic data
Wilding et al. (1989) [130]	Levodopa	T	^{111}In resin	5M	MB	Correlation of position and disintegration of tablet to peak plasma concentration	Plasma levels were fitted to gastric emptying data
Wilson et al. (1989) [131]	Ibuprofen	T	^{111}In resin	6M/5F	Fa/LB/HB	Correlation of position and disintegration of tablet to plasma concentration	Disintegration of tablet in the colon correlated with second peak in the plasma
Borin et al. (1990) [132]	Ibuprofen	T	^{171}Er oxide	8M-H	MB	Correlation of position and integrity to bioavailavility	Difference in GI transit had little effect on drug bioavailability
Davis et al. (1990) [133]	Indomethacin	T	^{111}In resin	6M-H	Fa/LB	The affect of food on bioavailability	Bioavailability same fasted and fed, drug well absorbed from the colon
Dennis et al. (1990) [134]	Ketoprofen	C	^{99m}Tc resin	7M-H	LB	Correlation of gastric spread to rate of drug absorption	Delay in gastric emptying led to a delay in drug absorption
Digenis et al. (1990) [59]	Erythromycin	MU	^{153}Sm oxide	7M	Fa/MB	Correlation of position and integrity of dosage form to plasma concentration	Pellet erosion and drug absorption began after gastric emptying
Graffner et al. (1990) [135]	Remoxipride	MU	^{111}In colloid	8M-H Fa	MB	Correlation of dosage form position to serum concentration	Drug absorbed throughout the GI tract including the large intestine
Healey (1990) [136]	5-ASA	T	^{111}In resin	8M/5F-P	LB	Tablet disintegration and onset of absorption	Tablet disintegration closely correlated with onset of absorption
Devane et al. (1991) [60]	Nifedipine	T	^{153}Sm oxide	8M-H	Fa	In vivo disintegration and the effect on plasma concentration	Correlation between absorption behaviour and tablet disintegration
Hardy et al. (1991) [13]	Naproxen	MU	^{153}Sm oxide	8M-H	Fa/MB	Disruption of pellet coating and onset of absorption	Close correlation between tablet coat disruption and detection of drug in plasma
Wilding et al. (1991) [14]	Levodopa	T	^{111}In resin	5M-H	MB	The effect of food on absorption from two novel formulations	Intersubject variation in L-Dopa absorption. The effect of transit/disintegration on subsequent absorption.
Wilding et al. (1993) [137]	Naproxen	T	^{111}In resin	12M-H	LB	In vivo performance of enteric coated tablets	Close correlation between tablet coat disruption and detection of drug in plasma
Wilding et al. (1991) [138]	Carbamazepine	O	^{111}In resin	8M-H	LB	Correlation of position in the GI tract with plasma concentration	Intrinsic crossover design using stable isotope technology. Decreased absorption from the colon.
Wilding et al. (1992) [139]	Captopril	C	^{111}In resin	8M-H	Fa	Pulsed release delivery and site-specific absorption	Absorption of captopril from different regions of the GI tract

* Key to abbreviations. Formulations: C, capsule; T, tablet; MU, multiple-unit dosage form; O, Oros system; S, suspension. Subjects: M, male; F, female; H, healthy volunteers; P, patients; X, not stated in original paper. Label: Tc, technetium; In, indium; Sm, samarium; I, iodine; Er, erbium. Dietary state: Fa, fasted; LB, light breakfast; MB, medium breakfast; HB, heavy breakfast; B, breakfast.

SIT of the enteric coated formulation was the same on both occasions. The onset of absorption of the drug was fastest for the uncoated formulation and slowest for the pellets taken after breakfast. The total amount of drug absorbed was unaltered by coating or the feeding conditions.

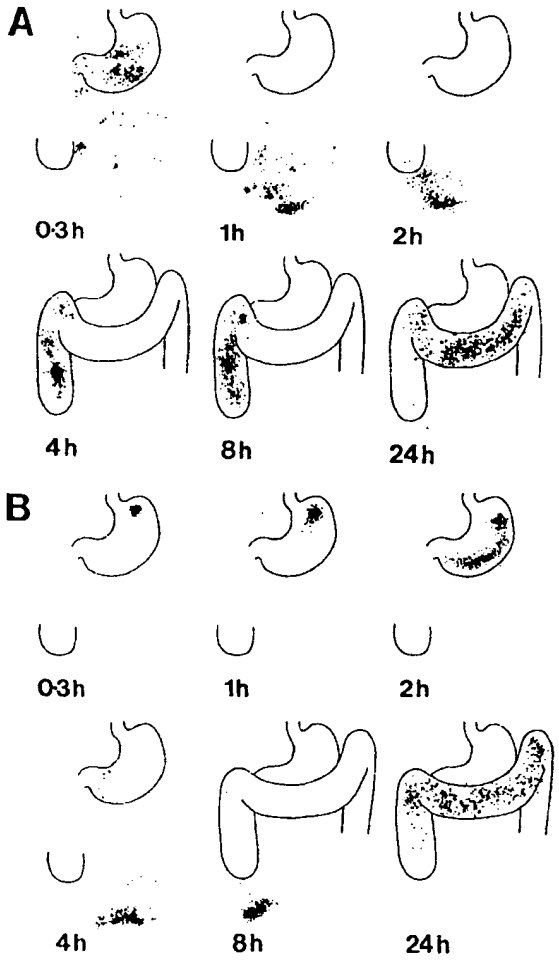

Fig. 2. Gastrointestinal transit of the ^{13}Sm-labelled naproxen pellets dosed to the same subject under fasted and fed conditions. A, fasted; B, fed.

4.2. Relationship between the systemic absorption and the gastrointestinal transit after the simultaneous oral administration of 20/200 Carbamazepine (CBZ) Oros and a ^{15}N-CBZ suspension to healthy volunteers (Ref. [138])

Carbamazepine (CBZ), an anticonvulsant drug, is presently given orally as either a conventional or slow release formulation. CBZ has a narrow therapeutic window and recently a 20/200 CBZ Oros

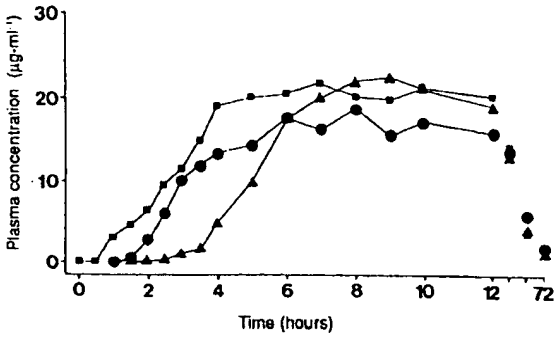

Fig. 3. Median plasma concentrations of naproxen after dosing with the uncoated formulation (■), and the enteric-coated formulation under fasted (●) and fed (▲) conditions.

controlled-release osmotic pump system was developed to reduce the fluctuations in the plasma concentration/time profiles.

A single-dose cross-over study with CBZ has been *performed on one study day*, using stable isotope technology and a gas chromatography-mass spectrometry analytical procedure. The 'intrinsic cross-over' design has important advantages over the alternative conventional cross-over design in that the problem of intrasubject variability between the different study days is avoided, the study can be performed over a shorter period of time and fewer blood samples have to be withdrawn from each volunteer.

A combination of γ-scintigraphy and pharmacokinetic evaluation was used to relate the position of the formulations in the GI tract to drug absorption. Plasma drug concentration – time profiles after the single oral administration of a suspension of CBZ and a 20/200 CBZ Oros osmotic pump system were determined simultaneously in eight healthy male volunteers. The oral suspension contained 100 mg CBZ labelled with the stable isotope ^{15}N and the Oros contained 200 mg unlabelled CBZ. The suspension was administered with 100 ml of water which contained 4 MBq of ^{99m}Tc DTPA to permit an outline of the GI anatomy to be established.

The Oros system was labelled by the incorporation of 1 MBq ^{111}In labelled ion-exchange resin powder

into an adhesive which was coated onto a small area around the edge of the system. The in vitro release profiles of labelled Oros systems resembled closely those of the unlabelled form, indicating that labelling of the Oros with ^{111}In did not affect the release of drug from the system.

The Oros systems were administered after breakfast and gastric emptying occurred between 1.1 and more than 11 h post-dosing (median, 5.3 h). SIT times ranged from 1.5 to more than 3.6 h with a median of 2.2 h. There were wide individual variations in colonic transit, and the total transit time ranged from 10 to 60 h (median, 22 h).

Relative systemic bioavailability of CBZ from the Oros system was reduced compared to the suspension. When the data were corrected for the amount of drug actually released from the system, the mean bioavailability was 85%.

Input functions generated to illustrate the in vivo absorption of drug into the systemic circulation from the Oros system, demonstrated that absorption of CBZ was rapid when the Oros was present in the stomach and small intestine. This finding indicates that the rate of absorption was determined by the release of drug from the system. Deviations from the predicted in vivo delivery rate were more apparent when the system entered the colon. In most subjects there appeared to be decreased absorption of CBZ from the Oros when the system was located in the colon. Some representative results for three of the eight subjects are shown in Fig. 4 and Table 4. Note the spread in the total transit time from 10.5 to 60 h.

4.3. Gastrointestinal transit and systemic absorption of captopril from a pulsed-release formulation (Ref. [139])

Captopril is an orally active ACE inhibitor that is quite well absorbed from the proximal SI. In healthy fasting subjects approximately 70% is absorbed but bioavailability is decreased by 25–50% when administered with food.

The development of a once daily captopril oral formulation would be of significant advantage. However, if the drug is only absorbed from the (proximal) SI, any form of CR system could display poor absorption characteristics at longer time periods when the system had passed into the distal (colonic) regions. Therefore an investigation was carried out in order to determine whether captopril is absorbed from the human colon. A novel pulsatile delivery system (Pulsincap) was employed. A 5-h pulse was selected on the basis of previous work, that indicated that an SU system administered to a fasted subject should reach the colon by this time. The absorption of the drug was followed in 8 fasted subjects by measuring free captopril levels in serial blood samples. Control experiments were performed using a conventional captopril tablet designed to release the drug in the stomach.

The pulsatile delivery system was filled with 25 mg captopril powder and 5 mg ^{111}In (1 MBq) labelled DTPA. The radioactive marker allowed the device to be visualized in the gastrointestinal tract and the in vivo release properties determined.

In six of the subjects the device reached the colon before the drug was released; the average time of colon arrival was 235 min. The in vivo pulse release values ranged from 246 to 389 min with a mean of 326.5 min (median 327.5) (Fig. 5). This value is in good agreement with that recorded in vitro and demonstrated the utility of the pulsatile system, combined with scintigraphy, for investigating drug absorption in different regions of the gastrointestinal tract.

The blood level profiles for free captopril demonstrated the expected profile for pulsatile release in correspondence with the in vivo release data, but not for all subjects. Only three out of the eight subjects demonstrated measurable levels of drug. Control studies with the conventional tablet formulation indicated that the subjects displayed typical pharmacokinetics (ADME) for captopril. The study showed that captopril can be absorbed in sufficient amounts from the terminal ileum/caecum but not in all subjects. Instability of the drug and possible metabolism by colonic microflora may account for the observed variability.

4.4. Characterisation of the in vivo behaviour of a controlled-release formulation of levodopa (Sinemet CR) (Ref. [14])

Levodopa in combination with carbidopa is an important treatment in Parkinson's disease. However, some patients become disabled with progression of

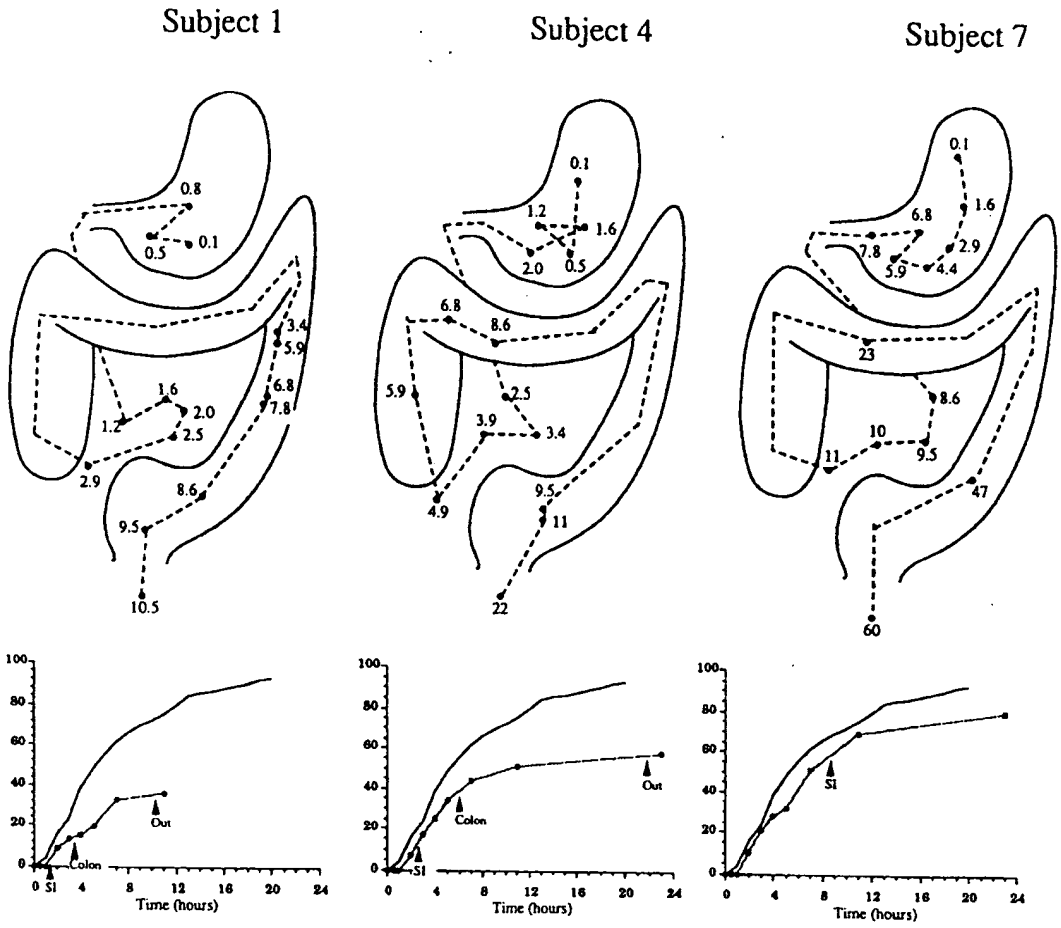

Fig. 4. Schematic representation of both the position of the Oros system in the GI tract (numbers indicate time post-dose in hours) and the in vivo absorption profile (time versus percent absorbed/released) for subjects 1, 4 and 7. (‾‾‾) percent absorbed versus time; (—) percent released versus time.

Table 4
Dose-normalized pharmacokinetic parameters following administration of 20/200 CBZ Oros

Subject	Area under curve ($0-\infty$) ($\mu mol \cdot h\ l^{-1}$ per mmol of dose)[a]	Peak concentration ($\mu mol\ l^{-1}$ per mmol of dose)	Oros/suspension ratio, area under curve ($0-\infty$)		Percentage dose recovered in voided Oros	Total transit time (h)
			[a]	[b]		
1	275	5.15	0.36	0.54	32.5	10
4	443	7.17	0.65	0.76	14.8	22
7	793	9.75	0.87	0.93	6.5	60

[a] Dose of Oros taken to be 200 mg.
[b] Dose from the Oros corrected for amount released.

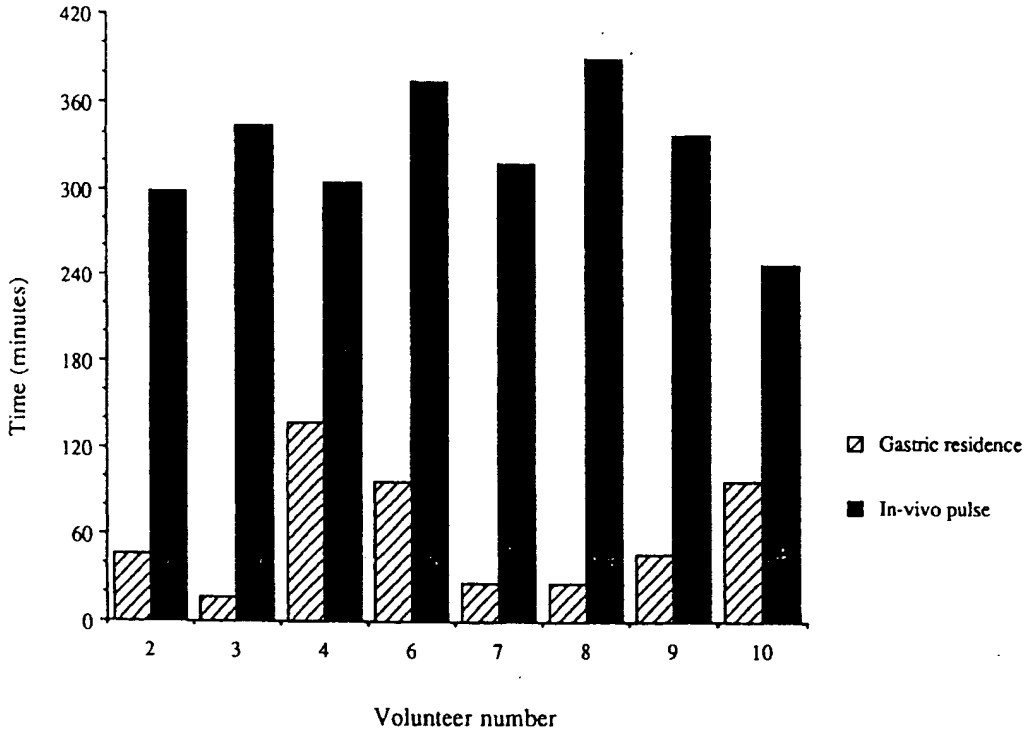

Fig. 5. Drug release and transit profile following oral administration of the pulsed release captopril device.

the disease by unpredictable 'on–off' effects in which they oscillate between akinetic and dyskinetic states, and they are particularly sensitive to the fluctuations in plasma levodopa levels that occur with conventional levodopa therapy. Thus, a formulation of levodopa that provided sustained concentrations of plasma levodopa may be of benefit and would also make therapy more convenient.

A study was performed using five subjects to correlate the transit and dissolution/disintegration behaviour of Sinemet CR in the GIT with the systemic absorption of levodopa using γ-scintigraphy. These parameters were compared with a standard Sinemet formulation in both the fed and fasted state. In addition, the subjects were concurrently given a radiotelemetry capsule that transmitted information on the pH in the different regions of the GI tract. The Sinemet CR formulation was labelled with a γ-emitting radionuclide (1 MBq of ^{111}In) by the incorporation of a small quantity (5 mg) of labelled ion-exchange resin. In vitro dissolution testing demonstrated that the presence of resin did not alter the controlled-release properties of the formulation and that the release of the drug from the erodible matrix system correlated with release of the radiolabelled resin. The standard Sinemet 25–100 (IR) tablets were manufactured in a similar manner with each tablet containing 2.5 mg of ^{111}In ion-labelled ion-exchange resin. The immediate release dosage forms were found to disperse soon after administration and empty rapidly from both the fasted and fed stomach. The erosion of the CR system was independent of both food and stomach pH. The tablet was observed to disintegrate fully in the GIT leading to complete release of levodopa over a 3–4-h time period. Close scrutiny and examination of the individual absorption profiles was possible due to the combined use of non-invasive scintigraphy and conventional pharmacokinetic assessment.

Considerable intersubject variation was found to exist for levodopa absorption. Drug absorption following administration of standard Sinemet in the

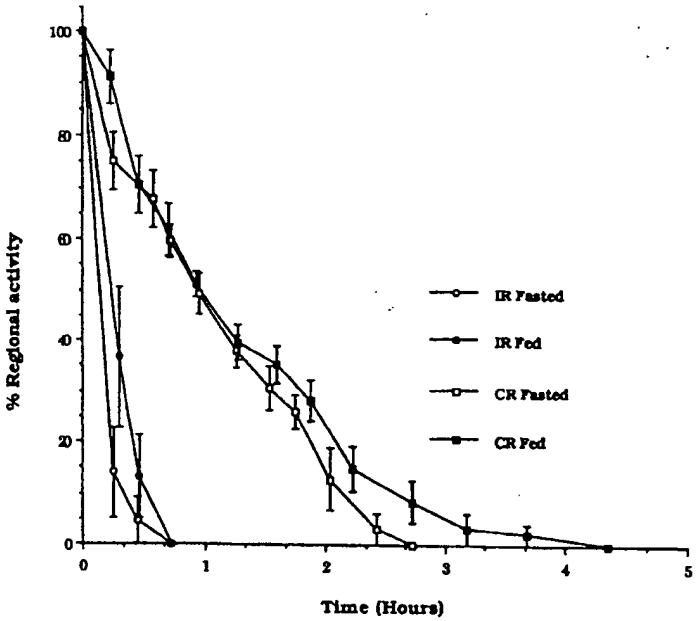

Fig. 6. The effect of food on the in vivo tablet disintegration profiles for Sinemet (25–100) (IR) and Sinemet CR 50–200 (error bars = S.E., $n = 5$).

fasted state was rapid with 50% of the dose being absorbed in the first 20 min. Post-prandial administration of the same formulation showed a similar rapid profile but with an initial lag phase due to a marginally slower in vivo tablet disintegration time and a lag time in gastric emptying, due to the redistribution of food. Levodopa absorption was more protracted with Sinemet CR than with standard Sinemet due to the controlled-release characteristics of the tablet matrix. There was no rapid initial absorption phase and instead, a gradual build up in the absorption profile occurred. The absolute bioavailability of levodopa from Sinemet CR, following administration after an overnight fast, was lower than that from standard Sinemet. A reduced bioavailability previously observed with Sinemet CR following administration was ascribed to the onset of phase III ('housekeeper wave' activity) which emptied the tablet from the stomach before total disintegration occurred. Rapid emptying reduced the dose available

Table 5
Gastrointestinal transit and pharmacokinetic parameters for sinemet (25–100) (IR) and sinemet (CR) (50–200) formulations

	Gastrointestinal transit (mean, in brackets: S.E.M.) ($t_{50\%}$, min)				Pharmacokinetic parameters (mean, in brackets: S.D.)	
	Gastric emptying	Colon arrival	SIT	Tablet disintegration time	Bioavailability (% of i.v.)	Ratio of 0–8 h urinary dopamine to levodopa recovery (ng h/ml)
IR fasted	28 (10.4)	232 (28.7)	204.2 (32.4)	9.2 (1.5)	80.4 (18.9)	0.10 (0.04)
IR fed	62.8 (16.4)	258 (34.5)	195 (34.4)	19.6 (4.4)	86.4 (16.5)	0.19 (0.05)
CR fasted	172 (15.1)	222.2 (13.3)	149.6 (9.7)	57.8 (3.3)	63.6 (14.3)	0.15 (0.09)
CR fed	103.4 (11.8)	310.8 (12.7)	207.4 (12.2)	61.0 (8.5)	71.0 (12.3)	0.20 (0.05)
I.v.	–	–	–	–	100	0.06 (0.04)

for absorption, since complete release of the drug did not occur before the tablet had passed the sites of maximum absorption.

The study demonstrated that release of levodopa could not be sustained beyond that of Sinemet CR without further reduction in bioavailability and increase in variability. Mean in vivo dissolution profiles obtained by the analysis of scintigraphic images are shown in Fig. 6. Mean GI transit data and pharmacokinetic parameters are provided in Table 5.

5. Conclusions

Regulatory authorities now require submitting organisations to provide information about the in vivo performance of sophisticated oral dosage forms within the GIT. γ-Scintigraphy provides a non-invasive means of acquiring such information under normal physiological conditions. The location of the radiolabelled delivery system and its integrity, dispersion or release characteristics within the body can be determined non-invasively using a γ-camera. Radiolabelling can be achieved, either by the direct incorporation of a radiolabelled compound into the preparation or by neutron activation of the dosage form that contains a non-radioactive tracer. The latter method avoids the need to handle radioactive materials during lengthy or complex formulation procedures and permits dosage form manufacture to be conducted under normal production conditions. The quantity of material needed to be incorporated into a formulation to render it suitable for use in a γ-scintigraphic study is very small and does not compromise the performance characteristics of the delivery system. The combination of γ-scintigraphy with conventional pharmacokinetic assessment (pharmacoscintigraphy) allows the distribution of a formulation to be related to drug absorption.

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